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A survey of patients with status epilepticus in a pediatric intensive care unit

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Abstract

Background: Status epilepticus (SE) is one of the major pediatric neurological events that requires pediatric intensive care. In this study, we reviewed patients admitted to a tertiary pediatric intensive care unit with status epilepticus in order to guide readers about the diagnosis, etiological factors, clinical signs, electroencephalographic properties, treatment protocols, duration of hospital stay, and complications. **Methods**: This study reviewed 88 presentations of status epilepticus in 64 patients between April 2015 and August 2016. These episodes were retrospectively reviewed for demographic properties, etiology, seizure type, neuroradiological and electroencephalogram (EEG) findings, recurrence rate, duration of hospital stay, treatment protocols, and factors affecting duration of intensive care unit stay. **Results:** The mean age of the study population was 6.17± 4.9 years. The female-to-male ratio was 30/34, which was not statistically significant. An analysis of the etiological factors showed that 1 (21.8%) of the cases was idiopathic SE; 26 (40.6%) were remote SE, 9 (14%) were febrile SE; 12 (18.7%) acute symptomatic SE; and 3 (4.6%) were progressive SE. Valproic acid and levetiracetam effectively controlled SE better than other antiepileptics, and this combination reduced midazolam infusion. Rectal diazepam administration before reaching hospital was found to be statistically significant for prevention of super refractory status epilepticus development ($p<0.05$). Additionally, when valproic acid or phenobarbital loading was administered as second-line treatment, the requirements for midazolam infusion reduced by a pronounced degree compared to levetiracetam. **Conclusion:** Though there are SE treatment protocols, no clear superiority was determined for antiepileptic agents used for loading in second-line treatment. With this study, we think some differences in patient management will contribute to improving outcomes.

Keywords: Status epilepticus, Pediatrics, Anticonvulsants.

INTRODUCTION

Status epilepticus (SE) is one of the most common neurological emergencies in children. Despite this, a definitive treatment protocol for status epilepticus has not been developed yet. Unfortunately, patients may still be undertreated due to various reasons such as providing patients with treatments aiming to reduce the number of seizures instead of totally eliminating them, and administration of inadequate anticonvulsant dose [1].

Timely treatment of status epilepticus prevents it from being treatment-resistant and provides a favorable effect on neurological development [2]. Whereas the evidence-based epilepsy protocol of the American Epilepsy Society was published in 2016, a target-specific treatment protocol was not defined, largely because there is a lack of multicenter comparative studies and the recent introduction of novel drug therapies [1].

OBJECTIVE

In the present study, the aim was to assess the diagnosis, etiological factors, clinical signs, electroencephalographic properties, treatment protocols, duration of hospital stay, and complications in order to guide emerging treatment protocols for SE.

MATERIALS AND METHOD

This study included 88 convulsive SE of 64 patients admitted to Kahramanmaraş Sütçü İmam University Research and Application Hospital, Pediatric Intensive Care Unit between April 2015 and August 2016. The reviewed parameters included patients' demographic properties, etiology, seizure type, seizure duration, number of antiepileptic used, imaging and electroencephalogram (EEG) findings, recurrence rate, duration of hospital and intensive care unit stay, treatment protocols, and factors affecting duration of hospital stay.

We called status epilepticus if a patient's epileptic activity time was more than 5 minutes and required second line therapy. The patients were grouped into 5 main groups based on SE etiology. Idiopathic SE (occurring in normally developed children), acute symptomatic SE (occurring in children that were neurologically healthy but developed SE triggered by trauma, central nervous system (CNS) infection, encephalopathy, or cerebrovascular events within last one week), febrile SE (prolonged epileptic activity secondary to fever with an axillary body temperature ≥38.3 °C, without any central nervous system infection), and remote symptomatic (occurring in patients with neurological impairment (cerebral palsy, CNS developmental disorder, hydrocephalus, genetic disorders) but no factor causing acute deterioration), and progressive SE (SE type occurring in cases with brain tumor, neurocutaneous disorders, and neurodegenerative disorders) [3].

Although the term resistant epilepsy is not based on a single parameter, the generally accepted definition is the inability to control seizures despite the use of two or more drugs in appropriate doses and durations, first as monotherapy and then in combination. Depending on seizure type and epilepsy syndrome, the likelihood of controlling seizure activity with a third drug following the use of the first two drugs is between 5% and 10%.4 Based on the definition of resistant epilepsy, the study population was categorized into two groups as those using more than 2 drugs and those using two or less drugs, and statistical analyses were performed accordingly.

All patients were monitored with a 2-channel EEG device. All underwent serum glucose, electrolyte, and arterial blood gas analysis, as well as serum drug level measurement in those who were on medications. After initial stabilization, patients who had no previous imaging studies or those who remained unconscious underwent brain magnetic resonance imaging (MRI) or computed tomography (CT) imaging. Depending on patient characteristics, serum drug level, toxicological screening, and cerebrospinal fluid (CSF) analysis were also performed. Patients who received thiopental or midazolam infusion were intermittently monitored with 12-lead ECG. The treatment protocol for SE below was applied after emergency care was given.

Treatment and monitoring protocol

First-line treatment:

All patients who had ongoing seizure after arriving at our hospital were administered midazolam at a dose of 0.1 mg/kg. When the patient had persistence of seizure activity after 5 minutes, a second midazolam push was administered at the same dose.

Second-line treatment:

Patients with persistent seizure activity 15 minutes after two doses of midazolam were administered phenytoin at a loading dose of 20 mg/kg. Patients who were unresponsive to phenytoin loading were administered a second loading dose of a different antiepileptic agent (in patients with a history of valproic acid, phenobarbital, or levetiracetam use, that agent was primarily selected). Phenytoin was loaded to all patients presenting with a first-ever seizure episode.

Third-line treatment: When seizure activity persisted despite second line treatment (60 minutes later), midazolam loading+maintenance treatment was commenced (maximum 0.8 mg/kg/hour). The patients were monitored with 12-channel EEG

Fourth line treatment:

Patients with ongoing seizure despite three lines of treatment

were begun on thiopental loading (5 mg/kg)+maintenance (5 mg/kg/hour infusion).

Statistical analysis

The relationships between antiepileptic drug use and treatment line was analyzed using the Chi-square test. All descriptive and analytic statistics were carried out using Statistical Package for the Social Sciences (SPSS) 19.0 software package. Parametric data were analyzed with one-way analysis of variance (ANOVA) test, and non-parametric data with Chi-square test. The study was approved by the Local Ethics Committee of Sütçü İmam University (Protocol number: 43, Decision Date: 01/31/2018).

RESULTS

The medical data of a total of 64 patients (34 males, 30 females) admitted to the pediatric intensive care unit with a diagnosis of status epilepticus were analyzed (Table 1).

Table 1: Demographic properties of the study population

Sex	64 (100%)
Girl	30 (47%)
Boy	34 (43%)
Age	64 (100%)
< 6 months	3 (4.6%)
6 m –12 m	3 (4.6%)
13 m – 24 m	20 (31%)
36 m – 60 m	12 (18.7%)
61 m – 120 m	13 (20%)
>121 m	13 (20%)
Radiological feature	49 (76.5%)
Normal	22 (44%)
Cortical dysplasia	6 (12%)
Cerebral Atrophy	13 (26%)
Brain edema + CNS infection symptom	3+4 (14%)
Isolated Corpus Callosum Agenesis	1 (2%)
EEG features	64 (100%)
Normal	28 (43%)
Generalized epileptic activity	10 (15%)
Focal epileptiform activity	14 (22%)
Secondary generalization	12 (19%)

CNS: Central nervous system, EEG: electroencephalogram

The mean age of the study population was 6.17 ± 4.9 years. Forty-nine (76.5%) patients underwent cranial imaging, which revealed normal findings in 22 (44%) patients, cortical dysplasia in 6 (12%), cerebral atrophy in 13 (26%), brain edema + CNS infection (brain edema indicated by flattening of the sulcus, leptomeningeal contrast involvement in addition to brain edema in a patient linked to streptococcus pneumonia, symmetrical bilateral thalamus, basal ganglion and periventricular white matter involvement in addition to edema in a case developing secondary to H1N1) in 3+4 (14%), and isolated corpus callosum agenesis in 1 (2%) (Table 1). Patients with normal MRI had normal EEG findings. During follow-up, all patients underwent EEG testing, with 28 (43%) having normal findings, 10 (15%) having generalized epileptic activity, 14 (22%) having focal epileptiform discharge, and 12 (19%) having secondary generalization (Table 1). Patients with febrile SE had normal EEG examination.

The patients were categorized by seizure duration, with 14 (21.8%) being categorized as idiopathic SE, 26 (40.6%) as remote SE, 9 (14%) as febrile SE, 12 (18.7%) as acute symptomatic SE, and 3 (4.6%) as progressive SE. Eighty-one percent of the patients did not have any relapse (Table 2). Among patients who were administered rectal diazepam at home or in the ambulance, the rate of needing third-line treatment was significantly less common in patients with resistant epilepsy ($P < 0.05$) (Table 3). In second-line treatment, on the other hand, a previously-used antiepileptic was given priority when information about medication use in the last 24 hours was unclear. Midazolam was less commonly required as the second-line treatment among patients who were loaded with a phenobarbital, when valproic acid was the first-line medication (Figure 1).

Table 2: Etiological classification

Idiopathic SE	**14 (21.87%)**
Remote symptomatic SE	26 (40.62%)
Febrile SE	9 (14.06 %)
Acute symptomatic SE	12 (18.75%)
Progressive SE	3 (4.68%)
Relapse yes/no	
No	52 (81. 2%)
Yes	12 (18.7%)

SE: status epilepticus

Table 3: Comparison of midazolam requirements between the groups with and without rectal diazepam use

	<3 antiepileptic drug users		≥3 antiepileptic drug users	
	Rectal diazepam administered	**Rectal diazepam not administered**	**Rectal diazepam administered**	**Rectal diazepam not administered**
1st-line treatment	1 (9%)	3 (8%)	1 (20%)	0 (0%)
2nd- line treatment	9 (82%)	27 (69%)	3 (60%)	2 (22%)
3rd-line treatment	1 (9%)	9 (23%)	1 (20%)	7 (78%)
Total	11	39	5	9
P value	0.592		0.040	

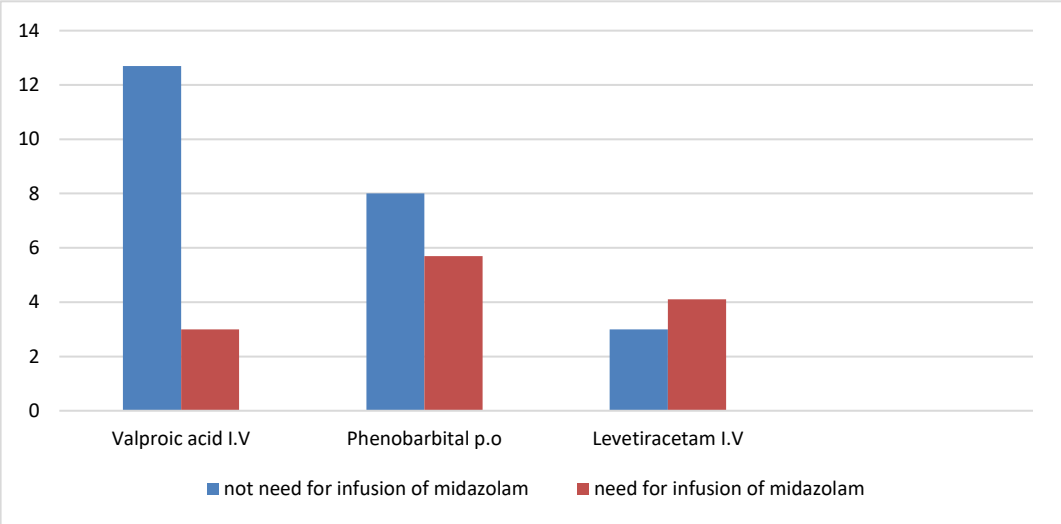

Figure 1: Assessment of medication efficacy in the second-line treatment

Table.4 presents the distribution of status epilepticus patients according to status of previous medication use and treatment line. The rate of needing third-line treatment was increased by a higher number of previously used medications, although this difference was statistically insignificant (P > 0.05).

Table 4: Relationship of multidrug users with the line treatments

	Never used drug	**1 drug users**	**2 drug users**	**3 drug users**	**4 drug users**	**5 drug users**
1st line	7 (24.1%)	3 (30%)	5 (45.5%)	6 (50%)	0 (0.0%)	0 (0.0%)
2nd line	22 (75.9%)	6 (60%)	6 (54.5%)	6 (50%)	0 (0.0%)	1 (0.0%)
3rd line	0 (0.0%)	1 (10%)	0 (0.0%)	0(0.0%)	1(100.0%)	0 (0.0%)
Total	29	10	11	12	1	1
P						
0.001						

Twenty-three patients underwent midazolam infusion for an average period of 0.31 ± 0.05 mg/kg/hours; seizure activity typically ceased with an infusion at a rate of 0.5 mg/kg/hour. Two patients with persistent seizure activity despite increasing the dose to a maximum of 0.8 mg/kg/h were put into thiopental coma.

The mean duration of stay on mechanical ventilation, in the intensive care unit, and hospital were 1.44 ± 0.64 days, 5.03 ± 1.02 days, and 9.19 ± 1.34 days, respectively. Duration of stay on mechanical ventilator, in intensive care, and hospital were significantly longer for patients that were administered a third-line treatment compared to those who were administered a first-line or second-line treatment ($P < 0.01$).

DISCUSSON

Fifty million people have a diagnosis of epilepsy worldwide, of which 33 million are children. It is estimated that 80% of children with epilepsy live in poor countries, and 70% of them are under the age of one year.5 As status epilepticus is a source of significant morbidity and mortality particularly in children, it is an important disorder for pediatric intensive care and pediatric neurology practices.

The prognosis of status epilepticus mostly depends on thepatient's age and duration and etiology of status epilepticus [6, 7]. Therefore, rapid termination of seizure activity, both clinically and electroencephalographically, reduces SE-related mortality and morbidity [8]. Although some studies reported an increased prevalence of SE among male children, many other studies showed that males and females are affected at the same rate [9-11]. In this context, our study was in accordance with literature data.

Prior studies have shown that the incidence of SE increases in the first 5 years, and it is more common in the first year of life [3]. Our study showed an increased SE incidence in the first 5 years of life, with the period between 12 and 24 months being more commonly affected.

Former studies have reported variable rates for various SE etiologies. Kumar *et al*. [10] reported that developed countries and developing countries showed dissimilarities from the etiological standpoint; they observed acute symptomatic SE at a rate of 47%, which most commonly included central nervous system infection. Many other studies reported similar findings [12, 13]. Additionally, Komur *et al*. [14] and Valencia *et al*. [15] reported that remote symptomatic SE had the highest incidence (52.8% and 38%, respectively). Our study demonstrated that remote symptomatic SE was the most common type, with an incidence of 40.6%.

Relapses most commonly occur as a result of underlying etiology, progressive nature of the disease, and stopping medication [3, 16]. Komur *et al*. [14] reported a relapse rate of 27% during 1-year follow-up, and attributed that finding to a greater percentage of remote symptomatic SE in their patient group. We demonstrated a relapse rate of 18.7%. We believe that novel antiepileptic drugs and parents using medications in a conscious and sound manner may have reduced that rate.

Pre-hospital treatment of status epilepticus reduces mortality and morbidity [1, 3, 14]. It was reported that rectal diazepam, buccal or nasal midazolam or oral clonazepam have equal efficacy, and one of these 3 applications are recommended [1]. As rectal diazepam is the only available agent in Turkey, it is recommended for patients with a history of epilepsy. Our study revealed that the need for a third-line treatment among the group using more than 3 drugs was lower among patients who were administered rectal diazepam than those who were not ($P < 0.05$). Furthermore, none of the patients using diazepam suffered respiratory depression. Chin *et al*. and Komur *et al*. reported that none of their patients using rectal diazepam needed third-line treatment or suffered respiratory depression [17, 14].

The cumulative findings of previous studies show that IV valproic acid and IV phenobarbital administered as second line treatment showed similar efficacy for terminating seizure activity but no adequate information was available for phenytoin and levetiracetam. Our study showed that IV valproic as the first line treatment and phenobarbital administered via nasogastric tube as the second-line treatment significantly reduced the need for third-line treatment. The efficacy of levetiracetam was found to be lower compared to phenobarbital and valproic acid. Phenytoin was excluded when comparing second-line treatments since it was administered to the treatment-naive patient group. Although the American Epilepsy Society guideline recommends phenobarbital via intravenous route, it is not available at our center as in many other centers, and thus we loaded it orally. A literature review revealed that Sudoh *et al*. [18] administered phenobarbital, initially via rectal or intramuscular then via oral route, and successfully eliminated seizures in a short time, and were then able to stop infusion treatments in 3 patients with SE refractory to midazolam infusion and phenobarbital infusion. They did not observe side effects in any of their patients. Another study supporting this view was reported by Kikuchi *et al*. [19], where 13 patients who had daily seizures despite receiving oral

antiepileptic drug or continuous midazolam infusion were administered rectal or high-dose phenobarbital. At the end of the study, 6 (46%) of 13 patients had their seizure frequency reduced and 2 (15%) completely abolished. However, 7 (56%) patients developed side effects that included dizziness, hypersalivation, emotional lability, and Steven Johnson syndrome. In a patient that suffered Steven Johnson syndrome the offending drug was stopped but others were continued. None of the patients suffered hypotension or respiratory depression.

CONCLUSIONS

We are of the opinion that pre-hospital use of rectal diazepam for the treatment of SE should be definitely recommended to families in Turkey. We observed that for second-line treatment after phenytoin, sodium valproic acid and phenobarbital were more effective among other antiepileptic agents.

We observed that as a second line treatment after phenytoin, sodium valproic acid and phenobarbital were more effective than levetiracetam. Additionally, an important finding in our study is that seizure duration dramatically improved after loading the drug already used by a patient when regular drug use could not be clearly ascertained. Nonetheless, additional studies are needed for aspects of status epilepticus that are not fully clarified.

Footnotes

- Authors' Contribution: Yasemin Coban was responsible for designing and conducting the study. Serkan Kirik and Olcay Güngör administered the study. Riza Dincer Yildizdas was the advisor of the research project.
- Conflict of Interests: The authors state that there is no conflict of interest in this study.
- Ethical Approval: Ethics committee of University of Kahramanmaras Sütcü İmam
- Funding/Support: The study was not funded by any institutions.

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